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OUR REFERENCE

REG/als/G20580WO

YOUR REFERENCE

PLEASE REPLY TO  
LONDON OFFICE

13 January 2005

European Patent Office  
(as International Preliminary Examining Authority)  
D-80298 Munich  
Germany

Dear Sirs

**Re: International Patent Application No. PCT/IB04/001583  
Clinovation**

We refer to the written opinion dated 4 November 2004 which issued in connection with the above application. In response thereto, we are filing herewith a demand for international preliminary examination and form PCT/IPEA/401 is enclosed herewith. The necessary fees are being paid via our deposit account. We are also filing, as set out hereinbelow, a response to the above-mentioned written opinion. We are also taking this opportunity (pursuant to Article 34 PCT) to file amended page 18 to replace the correspondingly numbered page presently on file. A copy of the page presently on file with amendments marked is enclosed for the examiner's assistance. The applicant is not, however, abandoning the deleted subject-matter from the present application and reserves the right to file one or more divisional or continuation applications in the national/regional phase or to reverse the Article 34 PCT amendments.

With regard to parts 1 and 2 of the opinion, we note the reference to D1 and D2 and with regard to the priority entitlement, we can confirm that the international application is an exact copy of the priority document.

With regard to part 3 of the opinion, claim 1 has been amended to incorporate the limitation of claim 4, namely that the short peptide linker has from 1 to 9 amino acid residues. Since the amendment has clear basis in the application as filed, we submit that no subject-matter has been added to the present application.

The examiner is of the view that claim 1 as originally filed lacks novelty over D1 or D2. The disclosure of these documents is similar in that both relate to the fusion protein expressed in baculovirus. One key difference between the disclosure of D1/D2 and that of the present invention is that the linker used in the present invention is shorter than that in D1/D2. The linker in D1 is described at page 5, lines 3-8. The DNA sequence of the linker is described in SEQ ID NO. 5 at page 5, line 5 of D1. The linker has 19 amino acid residues. The bracketed portion of the sequence describes the linker as consisting of three

glycine residues and one serine residue multiplied three times providing 15 amino acids. In addition, the Pst restriction endo-nuclease cleavage sites add another two amino acids and the Nde site adds another two amino acids. The four amino acids adjacent to the glycine/serine linker provide a total of 19 amino acids. Since amended claim 1 of the present application requires a carbon-nitrogen bond or a 1-9 amino acid residue linker, claim 1 of the present application is novel over D1.

Not surprisingly, precisely the same linker is disclosed in D2 at page 758, second column, line 10 and hence claim 1 of the present application is also novel over D2.

With regard to inventive step, and hence part 4 of the written opinion, we have the following comments. The applicant was aware of the disclosures of D1 and D2 and, indeed, reference has been made to this work at page 3, lines 1-3 of the present application. As indicated in the paragraph bridging pages 2 and 3 of the present application, several attempts have been made to associate the separate peptides of native Fel d 1 with only partial success. Both D1/D2 and the present invention provide fusion proteins in order to mimic the immunological function of native Fel d 1. The 19 amino acid residue linker in D1/D2 introduces a large number of additional residues compared to the size of chains 1 and 2 of the Fel d 1 protein. Indeed, antigen-presenting cells present larger peptides of this type (typically 12-20 amino acid residues in length) on MHC II molecules. Thus, the 19 amino acid residue linker in D1/D2 provides a significant risk of sensitisation to the linker during therapy.

In contrast, the present invention provides a short peptide linker, i.e. a carbon-nitrogen bond or 1-9 amino acid residues in length. This significantly reduces the risk of sensitisation to the linker during therapy. Moreover, since the native Fel d 1 protein comprises two separate chains, namely chain 1 and chain 2, it is particularly surprising that the confirmation of the recombinant peptide is maintained when the two chains are fused together with such a short linker. Surprisingly, however, the present applicant has found that a short peptide linker not only reduces sensitisation but also maintains the function of the Fel d 1 protein. We submit that, taking either D1 or D2 as a starting point, the skilled person would not consider reducing the length of the linker with any expectation of maintaining the immunological properties of the protein.

We note the examiner's comments at part 5 of the opinion and we propose deferring amendment of claim 19 until the national/regional phases.

At part 6 of the opinion, the examiner raises a number of objections with regard to lack of clarity and we shall address each in turn using the same numbering as the written opinion.

6.1 We have addressed this objection by defining the length of the linker in specific terms.

6.2 We should be grateful if we could defer amendment of the claims to address this objection until the national/regional phases.

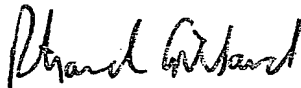
6.3 We are using the term "homology" in the claims to refer to the degree of similarity between different peptides. In this regard, we are enclosing herewith an extract from Chambers Dictionary of Science and Technology, page 567 which defines homology, in the biological sense as "[o]f DNA sequences of peptide sequences, the degree of similarity".

SEQ ID NO. 1 defines a specific protein although the primary structure of chains 1 and 2 of Fel d 1 are known to be variable. Indeed, several variants of the protein are referred to at page 2, lines 18-23 of the present application. Since a key feature of the present application is the length of the linker, we do not believe that a limitation in claims 8 and 9 to the specific sequence of SEQ ID NO. 1 is appropriate. Particularly since we have identified particular homologous proteins in the description and indicated preferred degrees of homology in claim 10, we believe that such a description of the protein would be clear to the skilled person. We have further specified that the homologue should provide "substantially the same allergenic properties as SEQ ID NO. 1" and we submit that the scope of this claim is therefore commensurate with the contribution the applicant has made to the art. We would, however, be prepared to define the homologue in terms of a percentage homology should the examiner believe this to be appropriate.

6.4 We should be grateful if we could defer amendment in this regard until the national/regional phases.

We should also be grateful if we could defer amendment of the description, including the amendment indicated at part 7 of the opinion, until the national/regional phases.

Yours faithfully  
Elkington and Fife LLP

A handwritten signature in dark ink, appearing to read "Richard Gillard", written in a cursive style.

Richard Gillard



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**Eingereichte Unterlagen**

**Items filed**

**Pièces envoyées**

Anmeldungs- (und Direktions-*) Nr./Patent Nr. Application (and Directorate*) No./Patent No. N° de la demande (et de la direction*)/n° du brevet	Ihr Zeichen Your reference Votre référence	ggfs. Art und Datum der Unterlagen** Nature and date of items (optional)** Nature et date des pièces (facultatif)**
1 PCT/IB04/001583	REG/G20580WO	Letter dated 13 Jan. 2004
2		with new page 18, guide copy,
3		dictionary extract and
4		Demand for IPE
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\* falls bereits bekannt

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## Claims

1. A recombinant Fel d 1 fusion product comprising a Fel d 1 chain 1, a Fel d 1 chain 2 and a linker selected from a carbon-nitrogen bond or a peptide linker having from 1 to 9 amino acid residues which links the N-terminal amino acid of one chain to the C-terminal amino acid of the other chain.
2. A fusion product as claimed in claim 1, wherein the linker links the N-terminal amino acid of the chain 1 to the C-terminal amino acid of the chain 2.
3. A fusion product as claimed in claim 1 or 2, wherein the linker is a carbon-nitrogen bond.
4. A fusion product as claimed in claim 1 or 2, wherein the short peptide has from 1 to 5 amino acid residues and preferably from 1 to 3 amino acid residues.
5. A fusion product as claimed in any preceding claim, wherein the linker comprises a target site for a reagent capable of selective cleavage of the linker.
6. A fusion product as claimed in claim 5, wherein the reagent is an enzyme.
7. A fusion product as claimed in any preceding claim, wherein the chain 1 and the chain 2 are covalently bonded together by one or more disulfide bridges into an antiparallel arrangement.
8. A fusion product as claimed in any preceding claim, wherein the Fel d 1 chain 1 comprises a sequence of SEQ ID NO 1, or a homologue or fragment thereof which provides substantially the same allergenic properties as SEQ ID NO 1.
9. A fusion product as claimed in any preceding claim, wherein the Fel d 1 chain 2 comprises a sequence of SEQ ID NO 2, SEQ ID NO 3, or a homologue or fragment thereof

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*General Editor*

Professor Peter M B Walker, CBE, FRSE

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CHAMBERS

**Aero** Any system designed to guide an aircraft or aircraft carrier.

**aviour (Behav)** Navigational behaviour in a species, ranging from returning home after a long or other excursion, to the more complex task involved in large migrations.

**iso-, homoeo-, homoio-** (*Genrl*) Prefixes from *homoios*, same.

**(Bot)** Term describing a species in which the leaves in a seedling or shoot are very like those of the parent.

**(Zool)** Showing direct embryonic development cells.

**(Phys)** Term applied when rays are either spread through one focus.

**Zool)** Said of a type of tailfin, found in all the higher fish, in which the vertebral column extends upwards and enters the epichordal lobe, and is in size to the hypochordal lobe.

**deous (Bot)** Having a perianth consisting of 1 of the same kind, not distinguishable into petals.

**Chem)** Containing a ring composed entirely of the same kind.

**ria** (*Met*) A metabolic defect resulting in the homocystine (the oxidized form of cysteine, amino acid) in the urine.

**structure (Crystal)** Crystal form with only one bond (either ionic or covalent).

**Zool)** Said of teeth which all have the same structure.

**ception (Telecomm)** That using an oscillating signal, to, or locked with, an incoming carrier, to magnitude and improve demodulation. Also: *of an excited carrier*.

**sm (Zool)** In metameric animals, the condition all the somites alike. Adj *homoeomeric*. Cf *sm*.

**y (Med)** See *homeopathy*.

**c (Zool)** Having all the gametes alike.

**c sex (Biol)** The sex that is *homozygous* for the *g* chromosomes. Cf *heterogametic sex*.

**(Bot)** The simultaneous maturation of the stamens in a flower. Cf *dichogamy*, *protogyny*.

**Zool)** Inbreeding, usually due to isolation.

**is (Chem)** Said of a system consisting of only one system in which the chemical composition of any physically small portion are the same as of any other portion.

**is coordinates (Maths)** A system of co-ordinates in which any multiple of the co-ordinates of a point represents the same point, eg in line-co-ordinates the line  $(a,b,c)$  is the same as the line  $(ka,kb,kc)$ .

**is function (Maths)** An algebraic function such that the indices occurring in each term is  $x^3 + 2x^2y + y^3$ .

**s ionization chamber (NucEng)** One in which the walls and gas have similar atomic composition and hence similar energy absorption per unit mass.

**s light (Phys)** See *monochromatic light*.

**s radiation (Phys)** Radiation of constant frequency (monochromatic), or constant particle energy.

**s reactor (NucEng)** One in which the fuel and moderator are finely divided and mixed (or the fuel may be a liquid moderator) so as to produce an effective homogeneous core material. See *slurry reactor*.

**(Zool)** The type of reproduction in which the offspring resemble the parents.

**ion (FoodSci)** Reducing fat particles in an emulsion (milk, ice cream) to a common size to improve stability and texture.

**homogenization (Glass)** See panel on Glasses and glass-making.

**homogenizer (Phys)** A device in which coarse and polydisperse emulsions are transformed into nearly monodisperse systems. The liquid is subjected to an energetic shear.

**homogeny (Zool)** Individuals or parts thereof which are homologous. Adj *homogenous*.

**homograft (Immun)** Graft of tissue from one individual to another of the same species. Also *allograft*.

**homoiohydric (Bot)** Plants able to regulate water loss and to remain hydrated for some time (hours, days or years) when the external water supply is restricted, eg most terrestrial vascular plants, few of which can survive desiccation. Cf *poikilohydric*.

**homolimerous (Bot)** Descriptive of a lichen thallus which has an even distribution of algal cells through its thickness. Cf *heterolimerous*.

**homoioplastic (Zool)** In experimental zoology, said of a graft which is transplanted to a site identical with its point of origin, eg a skin graft to a skin site. Also *homoplastic*.

**homiosmotic (Ecol)** Of an aquatic animal, maintaining a relatively constant internal osmotic pressure. Cf *poikilosmotic*.

**homiothermal (Zool)** See *warm-blooded*.

**homokaryon (Biol)** Somatic cell hybrid containing separate nuclei from the same species.

**homologous (Bot, Zool)** Of the same essential nature and of common descent.

**homologous alternation of generations (Bot)** See *homologous theory of alternation* and *isomorphic alternation of generations*. Cf *antithetic theory of alternation*.

**homologous chromosomes (Biol)** Chromosomes that pair with each other during synapsis at *meiosis*, so that one member of each pair is carried by every gamete.

**homologous organs (Bot)** Organs which are equivalent morphologically and of common evolutionary origin but which may be similar or dissimilar in appearance or function.

**homologous series (Chem)** A series of organic compounds, each member of which differs from the next by the insertion of a  $-CH_2-$  group in the molecule. Such a series may be represented by a general formula and shows a gradual and regular change of properties with increasing molecular weight.

**homologous theory of alternation (Bot)** The hypothesis that the sporophyte is of a similar nature to the gametophyte and thus that vascular plants evolved from algae with an *isomorphic alternation of generation*. Also *homologous alternation of generation*. Cf *antithetic theory of alternation*.

**homologous variation (Bot)** The occurrence of similar variations in related species.

**homology (Biol)** Of DNA sequences or peptide sequences, the degree of similarity.

**homology (Bot, Zool)** Morphological equivalence, common evolutionary origin. n *homologue*. Cf *analogy*.

**homology group (Maths)** Important group used in algebraic topology.

**homomorphic (Biol)** Said of chromosome pairs which have the same form and size.

**homomorphism (Maths)** A structure preserving mapping from one group to another. If  $(G, \circ)$  and  $(H, \star)$  are groups with group operators  $\circ$  and  $\star$  respectively, then a homomorphism from  $G$  to  $H$  is a mapping  $\phi: G \rightarrow H$  which satisfies the condition  $\phi(x \circ y) = \phi(x) \star \phi(y)$  for all  $x, y$  in  $G$ .

**homomorphous (Bot, Zool)** Alike in form.

**homoplasma (Zool)** In tissue culture, a medium prepared with plasma from another animal of the same species as that from which the tissue was taken. Cf *autoplasma*, *heteroplasma*.

**homoplastic (Bot, Zool)** (1) Of the same structure and manner of development but not descended from a recent common source. (2) See *homoioplastic*. n *homoplasty*.

**homopolar (Chem)** Having an equal distribution of charge, as in a covalent bond between like atoms.

**homopolar generator (ElecEng)** Low-voltage dc generator based on Faraday disk principle which produces ripple-free output without commutation.

**homopolar magnet (ElecEng)** One with concentric pole pieces.

**homopolar molecule (ElecEng)** One without effective electric dipole moment.

**homopolymer (Biol)** DNA or RNA strand whose nucleotides are all of the same kind. Usually made enzymatically from a single nucleotide precursor.

**homopolymer (Chem)** A polymer in which all repeat units are identical. See panel on *Polymers*.

**homoscedastic (Stats)** Having the same variance (applied to sets of observations).

**homosexuality (Behav)** Sexual interest directed at members of one's own sex.

**homospory (Bot)** A species which produces only one type of a spore. Adj *homosporous*. Cf *heterospory*.

**homostyly (Bot)** The condition in which all the styles are the same length. Cf *heterostyly*.

**homotaxis (Geol)** A term introduced by TH Huxley in 1862 to indicate that strata or sequences of strata in different areas sharing the same fossil characteristics are not necessarily the same age. A faunal assemblage may originate in locality A, be gradually dispersed or migrate to locality B and eventually reach locality C. The strata accumulating at these three localities are *homotaxial* although not necessarily contemporaneous.

**homothallism (Bot)** The condition in which successful fertilization can take place between any two gametes from the same organism. It is analogous to self-compatibility in flowering plants. Also *self-compatibility*. Adj *homothallic*. Cf *heterothallic*.

**homothermous (Zool)** See *warm-blooded*.

**homotopic mapping (Maths)** Two continuous mappings  $f$  and  $g$  of a topological space  $A$  into a topological space  $B$  are said to be *homotopic* if there is a function  $F(x,t)$ , representing a continuous mapping of  $A \times I$  into  $B$  ( $I$  being the unit interval), for which  $F(x,0) = f(x)$ ,  $F(x,1) = g(x)$ , for all  $x$  in  $A$  and for  $0 \leq t \leq 1$ .  $f$  and  $g$  are also said to be continuously deformed into each other.

**homotypic (Zool)** Conforming to the normal condition. Cf *heterotypic*.

**homozygosis (Biol)** The condition of being *homozygous*.

**homozygote (Biol)** An individual whose two genes at a particular locus are the same allele, the individual having been formed by the union of gametes carrying the same allele. Adj *homozygous*. Cf *heterozygote*.

**homunculus (Biol, Med)** A dwarf of normal proportions; a mannikin or little man created by the imagination; a miniature human form believed by animalculists to exist in the spermatozoon.

**Honduras mahogany (For)** See *American mahogany*.

**hone, honestone (Geol)** Term applied to fine-textured even-grained indurated sedimentary rocks which may be used as oilstones for imparting a keen edge to cutting tools. Honestone has been largely replaced now by emery and silicon carbide products. Also *whetstone*.

**honey (FoodSci)** A natural sweet substance made by bees from nectar from the pollen of flowers. Nectar is a weak solution of sucrose and other sugars, converted by diastase in the bee's gut, to glucose and fructose. Bees create a honeycomb from beeswax and crystallize the sugars by driving off moisture by fanning their wings. Flavour depends on the predominant flower frequented by the bees but the basic composition of honey is fairly constant at 77% sugar, 17.5% water giving a supersaturated solution